4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-0284]

Pediatric Studies of Sodium Nitroprusside Conducted in Accordance With the Public Health Service Act; Availability of Summary Report and Requested Labeling Changes

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a summary report of the pediatric studies of sodium nitroprusside conducted in accordance with the Public Health Service Act (the PHS Act) and is making available requested labeling changes for sodium nitroprusside. The Agency is making this information available consistent with the PHS Act.

FOR FURTHER INFORMATION CONTACT: Lori Gorski, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 6415, Silver Spring, MD 20993-0002, 301-796-2200, FAX: 301-796-9855, email: lori.gorski@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Sodium Nitroprusside Summary Review

In the Federal Register of January 21, 2003 (68 FR 2789), sodium nitroprusside (SNP) was identified as a drug that needed further study in pediatrics. The approved labeling lacked adequate information on dosing, pharmacokinetics, tolerability, and safety information in pediatric patients from birth to 18 years of age who receive SNP for controlled reduction of blood pressure.

A written request (WR) for pediatric studies of sodium nitroprusside was issued on July 8, 2002, to Abbott Laboratories, the holder of the new drug application for sodium nitroprusside. FDA did not receive a response to the written request. Accordingly, the National Institutes of Health (NIH) issued a request for proposals to conduct the pediatric studies described in the written request in July 2004 and awarded funds to Duke University and Stanford University in September 2004 to complete the studies described in the written request.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) submitted clinical study reports for SNP. The two studies are:

- NICHD-2003-09-DR-SNP1: A randomized double-blind, parallel group, dose-ranging, effect-controlled, multicenter study of intravenous infusions of SNP in pediatric patients who require deliberate, controlled relative-induced hypotension for at least 2 hours.

- NICHD-2003-09-LT-SNP2: A multicenter, randomized, double-blind, placebo-controlled, parallel group study to determine the pharmacodynamics of sodium nitroprusside during the prolonged infusion in pediatric subjects. This study was a withdrawal to placebo study.

Upon completion of these pediatric studies, a report of the pediatric studies of sodium nitroprusside was submitted to NIH and FDA. In the Federal Register of October 3, 2012 (77 FR 60441), FDA announced the opening on August 31, 2012, of docket FDA-2012-N-0284 for submission of data from pediatric studies of sodium nitroprusside. The data submitted to the docket were submitted in accordance with section 409I of the PHS Act (42 U.S.C. 284m) and were the same data submitted to investigational new drug application 71,979, with the exception that personal privacy information had been redacted from the data submitted to the docket.

The sodium nitroprusside docket remained opened for public comment from October 3, 2012, through November 2, 2012. There were no comments submitted to the docket during that time, and a memorandum for the record stating such was posted to the docket on November 5, 2012.

During the review of the submission, the Division of Cardiovascular and Renal Products identified inconsistencies in subject numbers between the pharmacokinetic/pharmacodynamic (PK/PD) analysis set and the ITT-E (intent to treat-efficacy) population in the study report NICHD-2003-09-DR-SNP1 and notified NIH. In a meeting with FDA on November 29, 2012, NIH indicated that that they identified treatment assignment inconsistencies between the two datasets and provided a strategy for addressing the concern and performing reanalysis. The need for reanalysis resulted in suspension of the review as of November 29, 2012. The corrected datasets and reanalysis were provided to the Agency and submitted to the docket on September 26, 2013.

The key findings of this submission are:

- The blood pressure lowering effect of SNP was demonstrated in both of the trials.
- A higher proportion of patients in the high-dose group achieved target mean arterial pressure (MAP) compared to the lowest dose of 0.3 microgram/kilogram/minute (µg/kg/min). The time-to-target MAP was also significantly shorter for the high-dose groups.
- With a starting dose of 0.3 µg/kg/min, ~25 percent of patients achieved target MAP in 5 minutes. Maintaining on a stable dose of 0.3 µg/kg/min for 10 minutes resulted in ~50 percent of patients reaching target MAP. Hence, a starting dose of 0.3 µg/kg/min is reasonable. It should also be noted that it may be prudent to maintain the infusion rate for an additional 5 to 10 minutes before titrating.

• The proportion of patients with MAP reductions of >20 percent below target increased in a dose-dependent manner.

• The safety profile of SNP in both the trials was largely consistent with the expected events as a result of the underlying disease and preoperative setting. Only blood pressure reduction events were clearly drug- and dose-related.

• Even though only four neonates were studied in the trial, there is no expectation that the PK/PD relationship and the safety profile would be any different in this age group.

• The FDA Adverse Event Reporting System (FAERS) search (up to October 25, 2012) retrieved only 26 pediatric cases with SNP use. Of these, four cases of elevated carboxyhemoglobin associated with SNP treatment were reported. The Office of Surveillance and Epidemiology review outlines several reasons why these data cannot be used to calculate incidence of adverse events in the population.

• For this submission, one large site (N = 36 enrolled in Protocol NICHD-2003-09-LT-SNP2; Investigator: Dr. David Rosen) was inspected. The Office of Scientific Investigations recommends the data be accepted.

• As a part of the WR, long-term safety data and a 1-year followup period for patients enrolled in the trial were sought. Information from followup was not available in the submission. However, the value of such information is limited and is not expected to have an impact on the ability to overcome the labeling gap. The complete report can be found at docket number FDA-2012-N-0284.

II. Recommendation

The submission provides a reasonable algorithm for administration of sodium nitroprusside to allow its use in perioperative settings to achieve controlled hypotension for

pediatric patients from birth to 18 years. FDA's requested labeling changes are available on the FDA Web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm379088.htm and in the docket (Ref. 1).

III. Reference

The following reference has been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested person between 9 a.m. and 4 p.m., Monday through Friday, and is available electronically at http://www.regulations.gov.

1. FDA Requested Labeling Changes.

Dated: January 10, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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